REMARKS/ARGUMENTS

Status of the claims

Claims 1-19 are pending. Claims 5-7 are withdrawn.

Rejection under 35 USC § 103 - Schatzberg in view of Ademmer

The Examiner has rejected claims 1-4 and 8-19 as allegedly obvious in view of Schatzberg in view of Ademmer. According to the Examiner, Schatzberg teaches a method of ameliorating psychosis with a glucocorticoid receptor antagonist (GRA), and Ademmer discloses that interferon alpha (IFN-α) can result in "psychiatric symptoms," including depression and suicidal ideation. The Examiner concluded that the claimed methods of ameliorating the symptoms of psychosis associated with IFN-α therapy with a GRA are therefore obvious.

The rejection is based in part on the Examiner's broad interpretation of the term "symptoms of psychosis" in claim 1 to include the psychiatric symptoms described in Ademmer. In response to arguments that these symptoms are not intended by the term, the Examiner adopts the broad interpretation "absent evidence to the contrary."

The Examiner has also cited Shimizu *et al.* as evidence that IFN-α therapy was known to cause an increase in cortisol levels. The Examiner alleges that one of skill would therefore be motivated to use a GRA, since an increase in cortisol levels is known to cause psychosis (from Schatzberg).

Applicants respectfully seek to rebut the rejection. As explained in more detail below, the art was indeed aware that IFN-α could increase cortisol levels, but it was also known that this increase was **transient**, and that cortisol levels stabilize in a relatively short time. This transience is a crucial point, because the psychotic symptoms associated with IFN-α therapy generally do not arise for several months, ***well after cortisol levels have returned to normal.*** Thus, the prior art actually ***teaches away*** from treating the psychotic symptoms associated with IFN-α with a GRA. One of skill, aware of the pharmacological profile of IFN-α, would have no

reasonable expectation that cortisol levels would have any connection to IFN-α associated psychotic symptoms.

Legal standard

In *Graham v. John Deere Co.*, 383 U.S. 1, 17 (1966), the Supreme Court explained that analysis of obviousness requires a determination of the scope and content of the prior art, the differences between the prior art and the claims at issue, and the level of ordinary skill in the pertinent art. A *prima facie* case of obviousness requires evidence that one of skill in the art would have had a reasonable expectation of success in practicing the claimed invention at the time of filing (*see* MPEP § 2143.02).

Once a *prima facie* case is made, the applicant has two options: (i) rebutting the rejection by arguing that the *prima facie* case was improperly made or (ii) traversing the rejection, *e.g.*, by providing evidence of secondary considerations such as unexpected results (*see, e.g.*, MPEP § 2145). A *prima facie* case cannot be properly made where the art the prior art teaches away from the claimed invention.

As indicated by the Supreme Court in *Graham*, the ***totality*** of the prior art must be considered, including references that teach away from the claimed combination (*see* MPEP § 2141.02, part VI). Proceeding contrary to accepted wisdom in the art is evidence of nonobviousness (*see* MPEP § 2145, part X. D. and *W.L. Gore & Assoc., Inc. v. Garlock*, 721 F.2d 1540, 1551 (Fed. Cir. 1983)). As explained in the MPEP § 2143.01, part II:

> The test for obviousness is what the combined teachings of the references would have suggested to one of ordinary skill in the art, and all teachings in the prior art must be considered to the extent that they are in analogous arts.

The courts have warned against picking and choosing from any one reference only so much of it as will support a given position, to the exclusion of information necessary for the full appreciation of what the art fairly suggests. *See, e.g., In re Lunsford*, 357 F.2d 385 (CCPA 1966).

The art teaches away from using a GRA to treat psychotic symptoms

At the time of filing, it was known that:

(i) treatment with IFN-α can result in a transient increase in cortisol levels ***and***

(ii) that psychotic symptoms associated with IFN-α therapy generally arise well after cortisol levels have stabilized.

Schatzberg further describes amelioration of psychotic symptoms caused by glucocorticoid regulatory dysfunction with a GRA (*see* Schatzberg, col. 1, lines 24-26, and Response mailed August 22, 2008, pages 8-9).

Cortisol levels fall to normal well before IFN-α associated psychotic symptoms arise, indicating that these symptoms are ***not related*** to cortisol. On the contrary, the fact that psychotic symptoms do ***not*** appear when cortisol levels are elevated strongly suggests that these symptoms are ***not*** related to glucocorticoid signaling. One of skill would therefore have absolutely no reason to link glucocorticoid regulatory dysfunction to the psychotic symptoms that can result from prolonged IFN-α treatment.

Applicants submit herewith a Declaration under 37 CFR 1.132 from Dr. Joseph Belanoff. In his declaration, Dr. Belanoff presents publications that describe the known effects of IFN-α treatment, including the transient increase in cortisol levels and the delayed onset of psychotic symptoms.

The increase in cortisol levels following IFN-α treatment is transient

In paragraph 6 of his declaration, Dr. Belanoff explains that cortisol levels in IFN-α patients return to normal soon after the initial administration. For example, Roosth *et al.* (**Ex. 1**) reported in 1986 that cortisol levels increase soon after IFN-α injection, but return to normal within 24 hours. Muller *et al.* (**Ex. 2**) confirmed this result in 1993. The report indicates that the IFN-α-induced cortisol elevation is transient, reaching maximal levels after 5.8 hours (*see* Table 2 on page 502).

Furthermore, with repeated administration of IFN-α, cortisol levels no longer respond to IFN-α. Gisslinger *et al.* **(Ex. 3)** reported that cortisol levels stabilize and remain normal in patients treated with IFN-α for three weeks. Gisslinger called it "IFN-α-induced adaptive changes in the HPA" (*see* Abstract).

Thus, Shimizu's disclosure of increased cortisol immediately after IFN-α administration does not fully represent the knowledge in the art at the time. The increase is a temporary phenomenon that disappears after 3 weeks of IFN-α therapy.

Psychotic symptoms arise, if at all, months after initiation of IFN-α therapy

One of skill might consider the transient increase in cortisol levels to be relevant to IFN-α associated psychotic symptoms if these events coincided in time. As explained by Dr. Belanoff, however, the psychotic symptoms generally arise much later in the course of IFN-α therapy, if at all. To quote, "psychosis is observed in <1.0% of the patients taking the drug and arises only after months of therapy" (*see* Declaration, paragraph 7).

Dr. Belanoff then presents four references, **Ex. 4-7**, that describe the onset of psychotic symptoms somewhere between 4 and 11 months. This time frame is well outside the three-week period disclosed by Gisslinger for the adaptive response to IFN-α, and stabilization of cortisol levels.

The art as a whole indicates that cortisol levels are not related to the psychotic symptoms associated with IFN-α therapy

The lack of psychotic symptoms observed during the time frame when cortisol levels are elevated, combined with the rarity of these symptoms, suggests that cortisol is unrelated to psychotic symptoms associated with IFN-α therapy.

In paragraph 8 of his declaration, Dr. Belanoff concludes that the art teaches away from the claimed methods. Essentially, one of skill would have no motivation to focus on the cortisol pathway as a cause of IFN-α-associated psychotic symptoms.

Schatzberg limits the types of psychoses that can treated by a GRA to those that result from glucocorticoid regulatory dysfunction. Schatzberg distinctly teaches that not all disorders with psychotic symptoms are included in that category (*see, e.g.*, Schatzberg, col. 7, lines 7-11).

Schatzberg does not link psychotic symptoms resulting from IFN-α administration to glucocorticoid regulatory dysfunction, and therefore does not provide a reasonable expectation that a GRA could successfully treat these symptoms. Ademmer and Deitrich also lack any suggestion that IFN-α is related to glucocorticoid signaling.

Shimizu links IFN-α administration to an increase in cortisol levels. Yet, as explained above, it was known to those of skill that the two phenomena do not occur at or near the same time.

Thus, there is still no evidence of an art-recognized connection between psychotic symptoms resulting from IFN-α treatment and glucocorticoid signaling. A fair reading of the combined prior art teaches away from the claimed methods, because the early increase in cortisol levels following IFN-α administration does not have a reported psychotic aspect. One of skill would more reasonably conclude that increased cortisol does ***not*** result in psychotic symptoms, because cortisol levels normalize well before psychotic symptoms arise.

The symptoms of psychosis recited in claim 1 are limited

On a tangential issue, Applicants note for the record that the symptoms of psychosis recited in claim 1 are limited by the claim language, and cannot be construed to read on all psychiatric conditions, as suggested on the bottom of page 8 of the Office Action.

Applicants therefore do not agree that the term psychosis would be interpreted to include depression and suicidal ideation, as described in Ademmer. The term psychosis is defined in the specification, *e.g.*, on page 4, lines 4-20. Neither the specification, nor the DSM IV (cited therein), associate these conditions with psychosis.

Summary

The prior art, described by Dr. Belanoff in his declaration, indicates that cortisol is not involved in the psychotic symptoms that result from IFN-α therapy. This is because cortisol levels normalize well before psychotic symptoms arise, if they arise at all. One of skill would therefore have no motivation to further reduce glucocorticoid signaling with a GRA in order to treat the psychotic symptoms resulting from IFN-α. In view of the foregoing comments, Applicants respectfully request withdrawal of the rejection under 35 USC § 103 over Schatzberg in view of Ademmer.

Rejection under 35 USC § 103 - Schatzberg in view of Ademmer and Dieterich

The Examiner has further rejected claims 18 and 19 based on Schatzberg, in view of Ademmer and Dieterich. According to the Examiner, Dieterich discloses that patients with HCV, HIV, and/ or drug use can experience neuropsychiatric side effects from IFN-α therapy.

Applicants respectfully traverse the rejection for the reasons stated above. Dieterich does not connect glucocorticoid signaling to the psychotic symptoms resulting from IFN-α treatment. Thus, one of skill would still lack a reasonable expectation of success in treating these symptoms with a GRA. In view of the foregoing, Applicants respectfully request withdrawal of the rejection under 35 USC § 103 over Schatzberg in view of Ademmer and Dieterich.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance and an action to that end is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 415-576-0200.

Respectfully submitted,

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Attachments: Declaration under 37 CFR 1.132
Ex. 1-7

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Ex 1

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Cortisol Stimulation by Recombinant Interferon-α_2

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Ex 1
1

Summary

Serum cortisol concentrations were determined by radioimmunoassay in cancer patients undergoing experimental therapy with recombinant interferon-α_2. Cortisol concentration rose steadily after interferon administration and was significantly different from that on control day at 8 h following intramuscular injection of interferon-α_2. Cortisol elevation was increased as weekly doses of interferon were increased ($0–120 \times 10^6$ units). Recent clinical trials of interferons for treatment of neurological and malignant diseases provide a compelling need to understand the actions and side effects of exogenously administered interferons.

Key words: *Cortisol stimulation – Interferon-α_2, recombinant – Serum – Tumor*

Introduction

Interferons are a class of proteins which act by inducing resistance to viral infection and by modulating the immune response (Friedman and Vogel 1970). It has recently been proposed that interferons may induce their effects via pathways similar to those of hormones (Blalock and Stanton 1980; Smith and Blalock 1981); and it has been demonstrated that like adrenocorticotropic hormone (ACTH),

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interferon stimulates a dose-dependent steroidogenic response by mouse adrenal tumor cells (Blalock and Harp 1981). The existence of a lymphoid-adrenal axis is suggested by the enhanced production of corticosteroids in normal (Solomon et al. 1967) and hypophysectomized mice (Smith et al. 1982) treated with interferon-inducing agents such as viruses. Likewise, humans who have undergone pituitary stalk resection (Van Wyk et al. 1960) respond to bacterial polysaccharide with elevation of the cortisol concentration.

The recent clinical trials of interferons for treatment of multiple sclerosis (Jacobs et al. 1981; Knobler et al. 1984) and of metastatic disease (Priestman 1983; Kirkwood and Ernstoff 1984) underscore the need for clarifying the in vivo consequences of administration of interferons to patients. Measurement of the plasma cortisol concentrations in individuals undergoing clinical trials with interferon-α_2 therapy for solid tumors demonstrated an increase in cortisol concentrations in these patients over a 24 h period.

Materials and Methods

Patients

The seven patients in this study ranged in age from 34 to 67 years with a mean ($\pm$SD) of 54.7 ± 12.6 years. All patients were informed and consented to experimental therapy for solid tumors with recombinant interferon-α_2 (Schering Corp., Bloomfield, NJ). Intramuscular injections of 0 (the diluent alone containing normal saline with 1 mg/ml of human serum albumin), 1, 10, 30, 60, or 120×10^6 units of recombinant interferon-α_2 were administered in ascending order to patients between 8:00 and 9:00 a.m. at weekly intervals over a 7-week period. Blood was drawn immediately prior to (0 h) and 1, 2, 4, 8 and 24 h post-injection. Two additional patients were studied hourly for a 24 h period after receiving injections of 10×10^6 units of interferon-α. These studies confirmed that sampling in other patients was adequate. Serum was frozen at $-70°C$ until cortisol assays were performed.

Because of the pyrogenic effects of interferon, patients received 650 mg of acetominophen (Tylenol) prior to and every 4 h post-treatment. The oral temperature of these patients was closely monitored.

Cortisol assays

Cortisol levels were determined by radioimmunoassay of ethanol-extracted serum samples. Antibody to cortisol was produced in rabbits (Cambridge Nuclear, Cambridge, MA) and [^{3}H]1,2,6,7-hydrocortisone (New England Nuclear, Boston, MA) was used as ligand. The complex was precipitated utilizing polyethylene glycol (Sigma Chemical Co., St. Louis, MO) in a modification of the technique described by Desbuquois and Aurbach (1971). Parallel dose-response curves for experimental serum samples and a cortisol standard were demonstrated over a 10-fold range. The intra-assay variability was 5.4% and the interassay variability was 5%.

Results

Timed measurements of cortisol concentrations in patients receiving interferon-α_2

The plasma cortisol concentrations in five patients injected intramuscularly with 120×10^6 units of recombinant interferon-α_2 were determined over a 24 h period. Fig. 1 illustrates the results of these experiments and compares them to four of the group when they received placebo. While the cortisol concentrations in patients receiving interferon-α_2 did not differ from placebo levels at 0 h, a trend toward elevated plasma cortisol concentrations in interferon-α_2-treated patients was evident at 2 and 4 h. By 8 h, cortisol concentrations in the placebo group ranged from 6.5 μg/dl to 13.3 μg/dl ($n = 4$) whereas in the group receiving interferon, cortisol concentrations ranged from 21.0 μg/dl to 48.1 μg/dl ($n = 5$); the measure was significantly different (8.6 ± 1.6 μg/dl and 31.3 ± 5.4 μg/dl respectively, $P < 0.005$). By 24 h post-injection, the cortisol concentrations in all patients had returned to pretreatment levels (12.2 ± 3.4 μg/dl). Two patients studied hourly documented that the peak cortisol concentrations occurred at 7 and 8 h after interferon injection (data not shown).

The oral temperature of these patients was monitored after placebo or interferon administration to assess the relationship of body temperature and cortisol concentration (Table 1). Prior to placebo injections, the mean ($\pm$SD) temperature was 36.9 ± 0.7°C and at 8 h had risen to 37.2 ± 0.2°C ($P > 0.05$, $n = 4$). On the day of interferon treatment, patients had temperatures of 36.6 ± 0.8°C prior to interferon injection and of 37.8 ± 0.8°C at 8 h ($P < 0.02$, $n = 5$). Although there was a

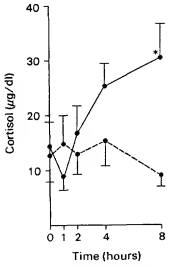

Fig. 1. Interferon-α_2 increases cortisol concentration in patient serum. Mean cortisol concentration in serum from patients receiving placebo (●- - - - -●, $n = 4$) or 120×10^6 units of interferon-α_2 (●———●, $n = 5$) are shown at various times post-inoculation. The Student t-test was used to determine significance (* $P < 0.005$) between the interferon and placebo groups for each time post 0 h.

TABLE 1

ORAL TEMPERATURE OF PATIENTS RECEIVING PLACEBO OR 120×10^6 U INTERFERON-α_2 [a]

	Time (h)				
	0	1	2	4	8
Placebo	36.9 ± 0.7 [b]	37.0 ± 0.3	36.9 ± 0.4	37.2 ± 0.2	37.2 ± 0.2
120×10^6 U IFN-α_2	36.6 ± 0.8	36.7 ± 0.5	36.6 ± 0.5	37.2 ± 0.5	37.9 ± 0.8

[a] These data are from the patients illustrated in Fig. 1. For placebo, $n = 4$ and for interferon-α_2 (IFN-α_2) treatment, $n = 5$.

[b] Data are expressed as mean ± SD.

significant difference in temperatures of patients at 8 h when compared to their 0 h temperatures, there was no significant difference between patients 8 h after receiving placebo and 8 h after receiving 120×10^6 units of interferon-α_2 ($P > 0.05$).

Cortisol concentrations are elevated by increasing doses of interferon

Because the peak effects on cortisol concentration regardless of dose of interferon-α_2 were seen at 8 h post-inoculation, this time point was chosen to delineate the effect of increasing doses of interferon-α_2 on glucocorticosteroid concentration. Table 2 shows the effects of varying doses of interferon-α_2 in seven patients on serum cortisol concentration 8 h post various doses of interferon. An elevation of cortisol was observed in all patients tested. For example, subject No. 5 exhibited a cortisol concentration of 8.8 μg/dl 8 h after placebo, 20.1 μg/dl after 10×10^6 units of interferon-α_2, and 48.8 μg/dl after 120×10^6 units of interferon-α_2. The dose of interferon which elicited the peak cortisol response differed in individual patients, but cortisol was elevated in all patients. When compared to the placebo group, the serum cortisol concentrations differed significantly in patients treated with 10×10^6 to 120×10^6 units of interferon-α_2 ($P < 0.05$ by one-way analysis of variance).

TABLE 2

SERUM CORTISOL (μg/dl) 8 h AFTER VARYING DOSES OF INTERFERON-α_2

Patient No.	Units of interferon-α_2 ($\times 10^6$)					
	0 (placebo)	1	10	30	60	120
1	6.2	12.7	31.0	n.d. [a]	23.2	23.3
2	15.2	15.2	n.d.	n.d.	32.7	39.8
3	11.8	13.8	18.9	35.2	34.5	n.d.
4	9.2	17.0	30.8	39.1	31.7	32.2
5	8.8	n.d.	20.1	n.d.	n.d.	48.1
6	7.6	32.7	30.6	19.2	19.3	21.0
7	7.6	9.4	31.4	n.d.	n.d.	n.d.
Mean ± SE	9.5 ± 1.2	16.8 ± 3.4 [b]	27.1 ± 2.4 [b]	31.2 ± 6.1 [b]	28.3 ± 3.0 [b]	32.9 ± 5.1 [b]

[a] n.d. = not done.

[b] $P < 0.05$ by one-way analysis of variance when compared to placebo.

Discussion

Patients treated with 120×10^6 units recombinant interferon-α_2 exhibited significantly elevated concentrations of serum cortisol within 8 h of treatment compared to placebo-treated patients. An enhanced serum cortisol concentration was no longer observed by 24 h post-treatment, indicating that the effect was transient. When patients were treated with increasing doses of interferon-α_2, there was a correspondingly enhanced concentration of cortisol.

It is not clear whether interferon-α_2 acts directly on adrenal cells to stimulate steroidogenesis, as does ACTH. The time course of stimulation is long (lasting many hours) compared to the rather rapid 2 h response seen in patients given intravenous synthetic $ACTH_{1-24}$ for assessment of adrenal function (Chamberlin and Meyer 1981). The acute rise after ACTH to a peak of 25 μg/dl to 35 μg/dl usually occurs between 30 min to 2 h after injection (Lee et al. 1973). It is also possible that interferon-α_2 mediates steroidogenic effects indirectly by stimulating pituitary or extra-pituitary release of ACTH. Another possibility which cannot yet be excluded is that the stress of fever may have contributed to the enhanced serum cortisol levels observed in these patients. However, the former explanation appears unlikely, because the oral temperature of patients receiving interferon did not differ significantly from those receiving placebo. That nonspecific stressors such as myalgias, arthralgias or fatigue caused cortisol elevation also seems unlikely since there appeared to be no difference in cortisol elevation between those patients reporting moderate to severe side effects when compared to those exhibiting mild side effects or having none. Regardless of the mechanism of interferon-α-action, cortisol concentrations in serum are significantly enhanced by 8 h post-injection.

Recent studies have indicated that interferon may have a steroidogenic effect when used at concentrations exceeding those required for an antiviral effect (Blalock and Harp 1981). The in vivo administration of agents which elicit an interferon response has also been reported to stimulate steroidogenesis, as indicated by elevated corticosteroid concentrations in both intact and hypophysectomised animals (Van Wyk et al. 1960; Solomon et al. 1967; Smith et al. 1982).

The direct or indirect steroidogenic effects of recombinant interferon-α_2 need to be documented carefully, because interferon therapy is now being tested in a variety of human diseases. Numerous side effects of interferon therapy, including neuropsychiatric manifestations (Adams et al. 1984), have been reported. Theoretically it is possible that elevated cortisol concentrations may account for behavioral changes. In addition, because glucocorticoids are powerful immune modulators (Claman 1975; Cupps and Fauci 1982) and the circadian variation in corticoid levels correlates closely with a bioperiodicity of the immune response (Abo et al. 1981; Kawate et al. 1981), careful timing of interferon treatment may allow enhancement of its therapeutic effects.

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Interferon-Alpha-2-Induced Stimulation of ACTH and Cortisol Secretion in Man

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EX2

Key Words. Interferon-α_2 · ACTH · Cortisol · Hepatitis B · Neuroimmune interactions

Abstract. Short-term effects of interferon-α_2 on plasma concentrations of adrenocorticotrophic hormone (ACTH) and cortisol were measured in man in relation to interferon absorption. Interferon-α_2 was given subcutaneously at a dose of 3×10^6 IU at 17.00 h to 2 female and 5 male patients who suffered from chronic hepatitis B infection and who had not previously been treated with interferon. Plasma levels of ACTH, cortisol and interferon-α were determined at 30-min intervals between 16.00 and 24.00 h. In each patient a similar cortisol, ACTH and interferon-α profile was determined on a day, when no interferon-α treatment was given. Interferon-α plasma levels peaked around 21.30 h, i.e. 4.7 h after injection. In each patient ACTH and cortisol levels were increased. As calculated from the areas under the curves, ACTH release was increased by an average of 332% (maxima at about 22.00 h, i.e. 5.2 h post injection); cortisol release was increased by an average of 311% (maxima at about 23.00 h, 5.8 h post injection). These actions were not related to side effects like fever or other flu-like symptoms. Our findings confirm that in man as in animals interferon-α_2 can act as a mediator between the immune and endocrine system.

There is evidence of bidirectional communication between the immune system and the hypothalamo-pituitary-adrenal (HPA) axis. Glucocorticoids inhibit or enhance immune functions, depending on concentration, time of application, cell type and species [1]. On the other hand, immunomodulatory substances can stimulate the HPA axis [2, 3]. The latter has been shown primarily in animals. Few investigations have studied the hormonal effects of cytokines in man with inconsistent results. Interleukin-2, interferon-γ or -α_2 have been shown to stimulate the secretion of cortisol in man [3–7]. Effects of the secretion of adrenocorticotrophic hormone (ACTH) have been registered in two studies using interferon-γ [5, 6] which did not significantly interfere with the release of ACTH. Moreover, from the data reported so far it cannot be excluded that stimulation of the HPA axis by cytokines is due to fever or other flu-like symptoms which may occur after administration of cytokines [8].

Interferon-α_2 is not only a physiologically relevant pleiotrophic lymphokine that is produced by monocytes or other leukocytes [9] but it is also a new therapeutic agent that is currently under investigation for the treatment of a number of diseases. Therapeutic efficiency has been shown for cancer [10], leukemia [11], hepatitis [12] or AIDS-associated Kaposi sarcoma [13].

The present investigation included patients suffering from chronic hepatitis B infection that had been selected for treatment with interferon-α_2. It was the aim of the study to look for time-dependent alterations in the secretion of ACTH and cortisol after drug administration in these patients. Moreover, skin temperature and heart rate were carefully monitored and the plasma levels of interferon-α were determined in identical blood samples withdrawn for the determination of ACTH and cortisol. Simultaneous quantification of hormone and interferon-α concentrations in the circulation have not been reported so far.

Patients and Methods

Patients

The study included 7 patients suffering from chronically active hepatitis B infection who were in a clinically stable state without signs of decompensation. They were treated with 3×10^6 IU recombinant human interferon-α_2 (Roferon A 3, Hoffmann-La Roche, Basel, Switzerland) 3 times a week for 4 months. Two women and 5 men, aged 26–69 years (mean ± SD; 49 ± 16.2; median, 53), were included. Written informed consent was obtained from all patients. The study protocol had been approved by the hospital ethics council.

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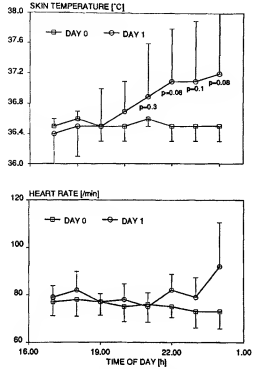

Fig. 1. Skin temperatures and heart rates in patients who received subcutaneous doses of 3×10^6 IU interferon-α_2 on day 1. Baseline measurements were performed on day 0, the day before drug administration. Values given are the mean ± SD obtained from 7 patients. Indicated p values were calculated by statistical comparison (ANOVA) of temperatures of day 0 and day 1.

Collection of Blood

On the day before treatment (day 0), and on the first day of treatment (day 1), blood was withdrawn between 16.00 and 24.00 h every 30 min for determination of ACTH, cortisol and interferon-α. Because of the chronic liver diseases and possible differences in the metabolism of hormones each patient was used as his own control on day 0 for registration of baseline secretion of hormones and interferon-α. At 17.00 h on day 1, a subcutaneous dose of 3×10^6 IU interferon-α_2 was injected. The time schedule of investigation was selected to reduce interferences with the well-known diurnal variations in cortisol and ACTH production.

To reduce stress effects, patients rested in bed from 15.00 up to 24.00 h. At 15.30 h a catheter was inserted into a forearm vein and kept open with physiological saline (30 ml/h). Blood was drawn through the catheter into chilled tubes which contained heparin for cortisol and interferon-α determinations or ethylenediaminetetraacetic acid (EDTA, 1 mg/ml) and 400 kIU trasylol for ACTH determinations. Plasma was prepared by centrifugation of the blood at 4 °C and it was stored frozen (–20 °C) until assayed.

Physiological Measurements

Blood pressure, heart rate and body temperature in the axilla were recorded every 60 min. Patients were requested to report flu-like symptoms every hour.

Determination of Hormones

ACTH and cortisol were determined using commercial radioimmunoassay kits: cortisol from Becton Dickinson, Heidelberg, FRG and ACTH from Nichols Institute, Bad Nauheim, FRG. The ACTH assay has a detection limit of 2 pg/ml and does not cross-react with ACTH fragments such as $ACTH_{1-3}$ (melanotropin), $ACTH_{1-17}$, $ACTH_{1-14}$, $ACTH_{34-39}$, endorphin or lipotropin [14]. The intra-assay coefficients of variation were 3–4% for cortisol and 5% for ACTH. Each series was analyzed in a single run to avoid interassay variations.

Interferon Assay

Interferon-α concentrations were determined with an enzyme-linked immunoassay as described previously [15]. This assay is based on the procedure established by Gallati [16]. It uses a monoclonal antibody that recognizes both interferon-α subtypes: interferon-α_1 and -α_2. The concentrations of interferon-α were calculated by comparing the extinctions of the samples with those obtained in assays with known interferon-α concentrations corresponding to the standard No. Gxa01-901-535 of the National Institutes of Health (NIH).

Statistical Test

Areas under curves (AUC) for ACTH and cortisol secretion over time were calculated from 18.30 to 24.00 h. Significance of differences in mean heart rates or skin temperatures after drug administration was determined by analysis of variance (ANOVA) and in hormone secretion between treated (day 0) and nontreated (day 1) patients by a paired t test. Differences were considered as significant for $p < 0.05$.

Results

Clinical Symptoms

The subcutaneous injections of interferon-α_2 were generally well tolerated and the low dose caused few side effects (fig. 1). Only 3 of the 7 patients developed temperatures exceeding 37 °C. In 1 patient it increased to 38.6 °C. The heart rates rose in those 3 patients, in 2 of them up to 120/min. Moreover, the 3 patients also complained of mild flu-like symptoms such as arthralgia, myalgia and fatigue. Blood pressure remained constant. There were no significant differences in temperature, heart rate or systolic blood pressure between day 0 and day 1 (fig. 1).

Interferon-α

Plasma levels of interferon-α began to increase within 1.5–3.5 h (mean ± SD, 1.9 ± 0.7; median, 1.5) with peaks at 2–7 h (mean ± SD, 4.7 ± 1.4; median, 5) after subcutaneous injection of interferon-α_2 at 17.00 h (table 1). Plasma peaks for interferon-α ranged from 1.0 to 11 IU/ml and plasma levels remained elevated until the end of the investigation at 24.00 h. In 3 noninjected patients the levels of interferon-α were up to 1.5 IU/ml (fig. 2).

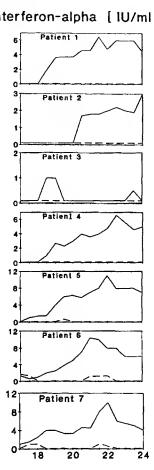

Fig. 2. Plasma levels of interferon-α in 7 patients injected with 3×10^6 IU interferon-α_2 at 17.00 h (——). Baseline levels were measured on the day before drug administration (— — —). Blood was withdrawn at 30-min intervals for the preparation of plasma samples.

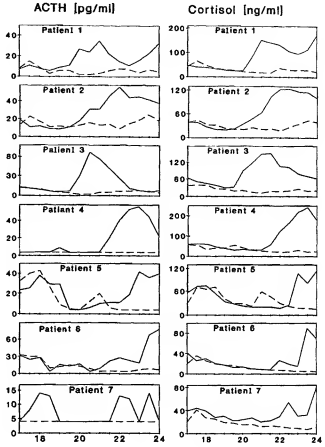

Fig. 3. Concentrations of ACTH and cortisol in the plasma of 7 patients who received subcutaneous injections of 3×10^6 interferon-α_2 (——) at 17.00 h. Baseline levels (— — —) were measured on the day before drug administration. For determination of hormonal profiles blood samples were withdrawn at 30-min intervals.

ACTH and Cortisol

The elevated plasma levels of interferon-α correlated with enhanced ACTH and cortisol secretion in each patient. It seemed unlikely that the hormonal responses to interferon-α were the result of nonspecific side effects such as the increase in heart rate or body temperature (fig. 1). The onset of the side effects was measurable later than the increase in hormone release. Moreover, the patients exhibiting the highest cortisol (patient 4) or ACTH (patient 6) response did not show those side effects. The beginning of the rise in ACTH release was highly variable; it occurred between 0 and 4 h after the increase in interferon-α plasma levels (mean ± SD, 2.1 ± 1.2; median, 2.5). Plasma peaks occurred between 3.5 and 7 h after interferon-α_2 injection (mean ± SD, 5.2 ± 1.1; median, 5) (table 1) ranging between 14 and 78 pg/ml (fig. 3). Cortisol followed ACTH increase within 0–30 min with plasma peaks between 4 and 7 h (means ± SD, 5.8 ± 1.1; median, 6.5) after interferon-α_2 injection (table 1). Peaks ranged from 81 to 242 ng/ml (fig. 4). There was no correlation of the height of interferon-α and ACTH or cortisol peaks. Some patients exhibited a slight increase in ACTH and cortisol immediately after inserting the needle (fig. 3). The plasma levels of ACTH and cortisol after interferon-α_2 application were significantly elevated between 18.30 and 24.00 h ($p < 0.05$, paird t test), as calculated from areas under curves (fig. 4).

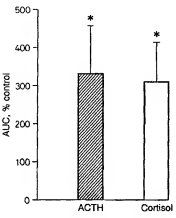

Fig. 4. Integrated AUC of ACTH and cortisol in the plasma of patients who were injected with interferon-α_2 as described in the legend to figure 3. AUC values were calculated from hormone levels between 18.30 and 24.00 h and related to the respective AUCs obtained from the hormone concentrations of the day before drug administration. Values given are the mean ± SD obtained from 7 patients. *$p < 0.05$, vs. control (paired t test).

Table 2. Maximal ACTH and cortisol response after interferon-α_2 administration in relation to maximal interferon-α levels in the plasma

Patient No.	Time of maximal plasma levels after s.c. injection of 3 × 10^6 IU IFN-α_2 for		
	IFN-α	ACTH	Cortisol
1	4.5	4.0	4.0
2	7.0	5.0	5.5
3	2.0	3.5	4.5
4	5.5	6.0	6.5
5	5.0	6.0	7.0
6	4.0	7.0	6.5
7	5.0	5.0	7.0
Mean value ± SD	4.7 ± 1.4	5.2 ± 1.1	5.8 ± 1.1

Values given are hours when plasma peaks occurred in individual patients and means ± SD. IFN = Interferon.

Discussion

The results show that acute doses of interferon-α_2 stimulate ACTH and cortisol secretion in man. The time pattern of ACTH increase observed after injection of interferon-α_2 was highly variable. Roosth et al. [7] and Scott et al. [17] reported an increase in cortisol production after intramuscular injections of interferon-α_2 in the morning with peak values after 8 h. This differs from our results in which cortisol peaks occurred between 4 and 7 h after injection. The difference might be due to time-dependent variations in the sensitivities of the ACTH/cortisol release system towards interferon-α_2. We chose the afternoon for interferon-α_2 application, since normally the release of HPA hormones remains rather constant between 16.00 and 2.00 h. ACTH peaks are rare between 18.00 and 24.00 h [18].

It seemed unlikely that the effects on ACTH and cortisol release were due to nonspecific stress, enhanced body temperature, heart rate or blood pressure, because only 3 of the 7 patients exhibited an increase in body temperature or heart rate whereas all patients showed elevated ACTH and cortisol plasma levels. This is in agreement with findings of other investigators who also failed to see significant changes in body temperature after interferon treatment [7] whereas Scott et al. [17] found an increase in temperature in all patients. Moreover, stress effects brought about by insertion of the needle are much more rapid in onset than the observed increases in ACTH and cortisol that were measurable after injection of interferon-α_2 and after the rise in interferon-α plasma levels.

There is little information about the mechanism of interferon-α stimulation of the HPA axis. Since interferon-α_2 is a polypeptide unable to penetrate the blood brain barrier, it is unlikely that it can enter the brain [19]. Smith et al. [20] could not find measurable concentrations of recombinant interferon-αA in the cerebrospinal fluid (CSF) of subjects within 48 h after intravenous injection of 18 × 10^6 IU recombinant interferon-αA. Only an infusion of 50 × 10^6 IU lead to a small increase in recombinant interferon-αA within the CSF of 3 of 4 patients. Rohatiner et al. [21] found low interferon-α levels in the CSF in only 1 of 5 patients who received 100 × 10^6 IU/m^2/day.

A second interpretation that must be considered concerns ACTH-like activity of interferon-α due to a structural relationship to ACTH as proposed by Blalock and Smith [22] thus interfering with the in vitro determination of ACTH. Blalock and Smith [23] used antibodies against the N-terminal end of $ACTH_{1-13}$. We used a two-site immunoradiometric assay. The assay detects only intact ACTH but not ACTH fragments such as $ACTH_{1-13}$ (melanotropin), $ACTH_{1-17}$, $ACTH_{1-24}$, $ACTH_{34-39}$, endorphin of lipotropin [14]. Moreover, in our study there was no quantitative correlation between interferon-α and ACTH. For example in patient 3 there was only a small increase in interferon-α (fig. 2) but a large increase in ACTH (fig. 3). On the other hand, patient 7 (fig. 2, 3) had high interferon levels but only a mild increase in ACTH.

The third possible mechanism that might be involved is the production of ACTH by lymphocytes. Lymphocytes are able to express the proopiomelanocortin gene and secrete ACTH [24, 25]. However, the time interval between stimulation of genomic activity of leukocytes by corticotropin-releasing hormone and maximal de novo synthesis of ACTH is 48 h [24], while the effects reported here were much more rapid.

Moreover, it must be assumed that some lymphokines seem to have CRH-like activity [26] although McGillis et al. [27] did not find ACTH release from cultured rat pituitary cells after stimulation with different cytokines including interferon-α. From the literature reported so far, it can therefore not yet be decided at which level lymphokines act upon the HPA axis. In spite of this limitation, however, it seems likely that alterations in HPA activity after cytokine treatment play a physiological role because different cytokines have distinct effects on the HPA axis: after application of low or high doses of interferon-γ, we and others found a cortisol increase without ACTH increase [5, 6] whereas acute doses of interferon-α_2 stimulated both, ACTH and cortisol release, a result similar to those seen in lower animals. The observed time pattern of hormone response seems more likely to be the outcome of a releasing effect on ACTH, or a preceding mediator, than of alterations in de novo synthesis.

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Interferon-α Stimulates the Hypothalamic-Pituitary-Adrenal Axis in vivo and in vitro

Key Words
Interferon-α
CRH
ACTH
Cortisol

Abstract
The successful therapeutic use of interferon-α (IFN-α) in myeloproliferative disorders offered the possibility to test its acute and long-term effects on the hypothalamic-pituitary-adrenal (HPA) axis in humans. ACTH and cortisol plasma concentrations were measured in 8 patients hourly starting from 4 p.m. through 12 p.m. on three occasions. The first time all patients were studied before initiation of therapy, when the vehicle was injected alone. The patients were studied again on day 1 of IFN-α therapy (5 million units) and once more after 3 weeks of therapy. On the control day, plasma concentrations of ACTH and cortisol were in the range expected for this time of day. In contrast, after the first administration of IFN-α a significant stimulation of the HPA axis was observed. After 3 weeks of IFN-α therapy, no significant stimulation of the HPA axis occurred after administration of IFN-α. IFN-α-induced adaptive changes in the HPA axis were also indicated by a significantly enhanced ACTH and cortisol response to exogenously administered supramaximal doses of corticotropin-releasing hormone (CRH) when the patients had been on IFN-α treatment for 3 weeks. To determine the exact locus of the IFN-α action, in vitro experiments were performed using rat hypothalamic organ and primary pituitary and adrenal cell culture systems. Thereby a significant stimulation of hypothalamic CRH secretion and rat adrenal corticosterone production was observed after INF-α at concentrations of 5×10^{-8} *M* or 10^{-7} *M* respectively. In contrast, no direct IFN-α effect on pituitary ACTH secretion could be observed in vitro. It is concluded that IFN-α stimulates the HPA axis. The locus of action seems to be the hypothalamus, as well as the adrenal glands.

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Several years ago, direct interactions between the immune and neuroendocrine systems were first described [1, 2], and the existence of a lymphoid adrenal axis has been postulated [3]. Further studies have attempted to elucidate this relationship between the immune and neuroendocrine systems [4–9]. Concerning the signals directed from the immune to the neuroendocrine system, the soluble mediator substances of the immune system – the cytokines – seem to be of particular interest. Various cytokines – interleukin (IL)-1, IL-2 and IL-6, as well as interferon (IFN)-α and IFN-γ – have been reported to activate the hypothalamic-pituitary-adrenal (HPA) axis [10–21]. The therapeutic use of IFN-α [22] in a variety of diseases offered the opportunity to test its effect in vivo in humans.

This study evaluated the effects of both acute and chronic IFN-α administration on the HPA axis in humans. In addition, the effect of IFN-α was tested in vitro in hypothalamic organ and in primary pituitary and adrenal cell culture systems.

Table 1. Characteristics of the patients treated with IFN-α

Pat. No.	Age	Sex	Diagnosis	Therapy
1	56	f	essential thrombocythemia	digoxin 0.1 mg spironolactone 50 mg bunitrole 5 mg
2	85	m	essential thrombocythemia	digitoxin 0.1 mg
3	66	f	polycythemia vera	digitoxin 0.1 mg
4	90	f	chronic myeloid leukemia	digoxin 0.1 mg dexpanthenylate 1 mg
5	69	f	chronic myeloid leukemia	
6	46	f	essential thrombocythemia	
7	52	m	essential thrombocythemia	nifedipine 40 mg atenolol 100 mg chlorthalidone 25 mg
8	72	f	polycythemia vera	digoxin 0.1 mg spironolactone 50 mg bufizide 5 mg piracetam 2,400 mg

Materials and Methods

In vivo Study

Eight patients with myeloproliferative disorders (table 1), who received IFN-α for therapeutic reasons [22], were studied on three separate occasions after informed consent was obtained. On day 1, patients received placebo; on day 2 the patients were injected recombinant human IFN-α (5 million units subcutaneously) (Berofor; Boehringer Ingelheim, FRG); and finally the patients were studied again after they had been on therapy for 3 weeks (5 x 5 million units/week). To minimize the effect of diurnal variation of ACTH and cortisol concentrations, all tests were started at 3.30 p.m. IFN-α or placebo was injected at 4 p.m. Blood was collected every 30 min until 5 p.m. and at hourly intervals thereafter until 12 p.m. In addition, a corticotropin-releasing hormone (CRH) test was performed in the same patients before starting the treatment and after 3 weeks of treatment. These tests were done 2–3 days prior to the 8-hour study described above, and the patients did not receive IFN-α on this day. All subjects were given 100 μg of the hypothalamic-releasing hormone for ACTH, i.e. CRH, in an intravenous bolus injection. For the benefit of a quiescent HPA axis, these tests were performed at 6 p.m. Blood was collected in prechilled EDTA tubes, immediately placed on ice and centrifuged within 2 h. Plasma was then separated and stored at –20 °C until assayed.

IFN-α plasma levels were determined using a cytopathic effect inhibition assay [23]. Test plasma were assayed for their ability to protect human A549 lung cancer cells from cytopathic effect induced by mouse encephalomyocarditis virus (EMC). In brief: the test cell line was incubated in microliter plates, and 2 or 3 days later they were treated with plasma samples or IFN overnight before challenge with EMC. The cytopathic effect after 2 days was scored under a microscope. IFN-α2c (specific activity 320 IU/ng), laboratory standard H812, calibrated to the international reference preparation G023-901-527 was used as positive control. The investigations were carried out in duplicate, the detection limit was 4 IU/ml.

ACTH was measured by a commercially available IRMA (Corti-Diagnostics BV, Apeldoorn, The Netherlands), cortisol by a RIA (Baxter, USA). Body temperatures was recorded whenever blood was drawn.

In vitro Studies

Male Sprague-Dawley rats weighing 200–250 g were sacrificed after CO_2 analgesia by decapitation. The hypothalamus, the pituitary gland and the adrenal glands were then removed for the respective organ or cell cultures.

Hypothalamic Organ Cultures. The hypothalamic region was removed with sterile scissors between the posterior border of the optic chiasma, the anterior border of the mammillary bodies and the lateral hypothalamic sulci as described previously [24]. Immediately after dissection, whole hypothalami were placed in 24-well plates (Costar, Cambridge, Mass., USA) at 37 °C in an atmosphere containing 5% CO_2. Each well contained 2 ml of Dulbecco's modified Eagle's medium (DMEM; Gibco, Paisley, UK), supplemented with 2% fetal calf serum (FCS) (Gibco) and antibiotics (Gibco). After 2 h preincubation, the hypothalami were moved from well to well at 20-min intervals. The first three wells consisted of medium alone, the next two wells of medium with varying concentrations of IFN-α or plain medium as a negative control, the next two wells again of medium alone, and the last

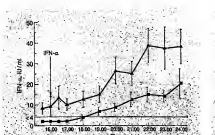

Fig. 1. Mean (± SEM) plasma IFN-α concentrations in patients with myeloproliferative disorders (■ = on day of first subcutaneous application of 5 million units IFN-α, ▲ = after 3 weeks of IFN-α therapy, 5 × 5 million units/week). The line across the bottom at 4 IU/ml IFN-α indicates the limit of detection of the assay used.

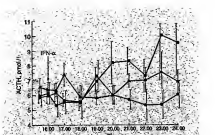

Fig. 2. Mean (± SEM) plasma ACTH concentrations in patients with myeloproliferative disorders (● = before IFN-α therapy, ■ = on day of the first subcutaneous application of 5 million units IFN-α, ▲ = after 3 weeks of IFN-α therapy 5 × 5 million units/week).

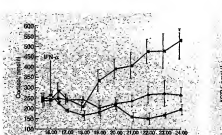

Fig. 3. Mean (± SEM) plasma cortisol concentrations in patients with myeloproliferative disorders (symbols are the same as in figure 2).

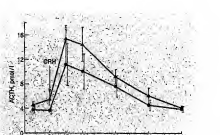

Fig. 4. Mean (± SEM) ACTH concentrations in patients with myeloproliferative disorders, before and after intravenous application of 100 µg CRH (● = before therapy with IFN-α, ▲ = after 3 weeks of subcutaneous therapy with 5 × 5 million units IFN-α/week).

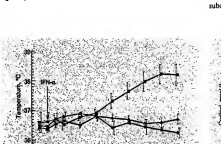

Fig. 4. Mean (± SEM) of axillary body temperature (°C) in patients with myeloproliferative disorders (symbols are the same as in figure 2).

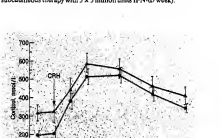

Fig. 5. Mean (± SEM) cortisol concentrations in patients with myeloproliferative disorders before and after intravenous application of 100 µg CRH (symbols are the same as in figure 5).

well of medium with 60 mM KCl for depolarization of the membranes to serve as positive control. Twelve hypothalami were used for each concentration, and hypothalami that failed to respond to KCl with at least a 70% increase of CRH release compared to basal release were excluded from analysis.

Pituitary Cell Culture. After dissection of the posterior and neurointermediate lobes, the anterior lobe of the pituitary gland was mechanically and enzymatically dispersed as described previously [24]. In short, the anterior lobes were first minced in Petri dishes and subsequently dispersed by a 20-min incubation with 0.1% collagenase type 4 (Sigma, St. Louis, Mo., USA) in DMEM. The pellets were washed twice by suspension and centrifugation at 160 *g* and resuspended in DMEM supplemented with 10% FCS. Cell yield was approximately 2×10^6 cells/gland and cell viability determined by trypan blue exclusion was always >95%. The cells were incubated for 4 days in a 24-well plate at a density of 5×10^5 cells/ml in DMEM with 10% FCS, 1% nonessential amino acids (Gibco) and antibiotics at 37 °C under 5% CO_2. The cells were then washed 3 times and incubated for 3 h with DMEM with or without IFN-α at concentrations ranging from 10^{-11} to 10^{-9} *M* in triplicate at 37 °C in an atmosphere of 5% CO_2. rCRH at a concentration of 10^{-9} *M* served as positive control. After incubation, the 24-well plate was centrifuged and the supernatant was collected and stored at –20 °C until determination of ACTH.

Adrenal Cell Culture. Adrenal glands were treated as described above for the pituitary gland. ACTH (Ciba, Basel, Switzerland) at a concentration of 10^{-9} *M* served as positive control for adrenal corticosterone release. Supernatants were stored at –20 °C until corticosterone was determined by RIA (ICN Biomedicals, Costa Mesa, Calif., USA).

Statistical Analysis

All results are expressed as the mean ± SEM. To evaluate a hormone response in vivo, the area under the curve was calculated by integration of the hormone levels in conventional units and time of testing in minutes. Comparing ACTH and cortisol plasma concentrations in vivo as well as body temperature (fig. 2–4), the statistical evaluation was done using one-way analysis of variance, because some patients did not have complete values for the 3 days of investigation. The statistical analysis of CRH test was done as before comparing the area under the curve using paired *t* test. To evaluate a hormone response in vitro, mean increases of the respective hormone release over baseline secretion at varying IFN-α concentrations were compared by the Kruskal-Wallis test. Significance was accepted at $p \leq 0.05$.

Results

In vivo Study (fig. 1–4)

IFN-α plasma levels on day 1 of IFN-α treatment, as shown in figure 1, increased after 3 h and reached the maximum after 6 h. The curve of IFN-α plasma concentrations after 3 weeks of IFN-α treatment ran parallel, but shifted to a higher level. Recombinant human IFN-α at a dose of 5 million units induced an increase of cortisol plasma levels (fig. 3) and led to an elevation of the body temperature (fig. 4). Compared to their normal pattern observed between 4 and 12 p.m. on the baseline day, when the patients received no IFN-α, ACTH plasma concentrations did not increase significantly (fig. 2) whereas cortisol plasma levels increased markedly, as expressed by a significant increase of the area under the curve ($p < 0.01$; fig. 3) after the first injection of IFN-α. The onset of this IFN-effect was seen after 3 h and plasma cortisol concentrations remained elevated thereafter until the end of the observation period of 8 h and thus paralleled the plasma concentrations of IFN-α shown in figure 1. When the patients were studied again after they had been on IFN-α for 3 weeks, only slightly but not significantly elevated ACTH and cortisol plasma levels compared to the baseline day could be observed. Body temperature increased after the first injection, which is also expressed by a significant increase of the area under the curve ($p < 0.05$; fig. 4) and returned to the baseline level after 3 weeks of IFN-α treatment.

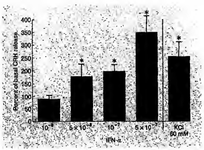

Fig. 7. Effect of graded IFN-α concentrations on the CRH secretion in primary rat hypothalamic organ cultures expressed as percent of control. KCl (60 m*M*) for depolarization of the cell membrane served as a positive control (*p < 0.05 compared to basal CRH release).

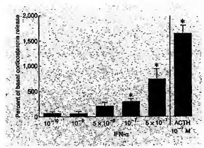

Fig. 9. Effect of graded IFN-α concentrations on the corticosterone secretion in primary rat adrenal cell cultures expressed as percent of control. ACTH (10^{-7} *M*) served as a positive control (*p < 0.05).

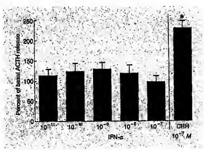

Fig. 8. Effect of graded IFN-α concentrations on the ACTH secretion in primary rat pituitary cell cultures expressed as percent of control. CRH (10^{-7} *M*) served as a positive control (*p < 0.05).

CRH Test (fig. 5, 6)

Despite the return of body temperature to the baseline level after 3 weeks of IFN-α, the area under the curve of ACTH plasma concentrations was significantly greater ($p < 0.01$) than on the baseline day. This significant difference ($p < 0.05$) could also be observed in the area under the curve of the plasma cortisol levels.

In vitro Studies

In the primary rat bypothalamic organ cultures, a significant dose-dependent increase of CRH release could be observed starting at IFN-α concentrations of $5 \times 10^{-8} M$ (fig. 7). In the primary dispersed pituitary cell cultures, no effect of IFN-α on ACTH release could be registered over an IFN-α concentration range from 10^{-11} to 10^{-7} *M* (fig. 8). In primary dispersed adrenal cells, IFN-α at a concentration of 10^{-7} *M* induced a significant increase of corticosterone release, which was still higher at 5×10^{-7} *M* IFN-α (fig. 9).

Discussion

This study demonstrates that IFN-α stimulates the HPA axis in vivo and in vitro. When patients received IFN-α for the first time a significant increase in plasma cortisol concentrations and body temperature was observed. Chronic subcutaneous application of IFN-α led to adaptive changes such that the cortisol response to IFN-α was clearly diminished. Furthermore, in the CRH test, where supramaximal doses of the hypothalamic releasing peptide are administered, increased ACTH and cortisol responses could be registered after 3 weeks of IFN-α therapy. A direct effect of IFN-α on the hypothalamus and the adrenal gland described here for the first time might be responsible for this activation of the HPA axis.

Since the rise of cortisol following administration of IFN-α is not as abrupt as after other known activators of the HPA axis, such as CRH, one might argue that the stimulation is either unspecific, e.g. caused by IFN-α-induced fever or through other mediators. Holsboer et al. [19], for instance, interpreted their observation of IFN-α-induced stimulation of the HPA axis in this way. A favorite candidate for a mediator substance involved in the mediation of the IFN-α effects would be the generation of other ILs by IFN-α, such as IL-1 and IL-6, which have both a pyrogenic and ACTH-releasing activity. Although elevation of body temperature as cause for the activation of the HPA axis cannot be totally ruled out, several points argue against this possible mechanism of action. First, in vitro a direct action of IFN-α on the hypothalamus and adrenal gland has been observed, and second, after chronic IFN-α administration the rise in temperature was abolished whereas the HPA axis was still activated, as expressed by the findings of the CRH test. Furthermore, a specific activation of the HPA axis through stimulation of hypothalamic CRH release unrelated to its pyrogenic effect has also been proposed for another cytokine, namely IL-1 [16]. In addition, the time course of the ACTH and cortisol curves followed the course of IFN-α plasma concentrations after subcutaneous injection.

The chronic activation of the HPA axis by IFN-α is reminiscent of the alterations seen in anorexia nervosa, depression, alcoholism and compulsive running [25], and could also be responsible for the neuropsychiatric disorders previously described in patients receiving treatment with IFN-α [26].

The previously reported inhibitory effect of IFN-α on insulin [27] and sex steroid production [28] in conjunction with the activation of the HPA axis would fit well into Selye's [29] concept of the stress reaction and the general adaptation syndrome. In order to optimally oppose a stressor, e.g. a severe infection, the organism, by elevation of IFN-α plasma concentrations, would activate endocrine systems like the HPA axis that has powerful desirable effects on the cardiovascular system and metabolism, and deactivate systems like the sex steroids, that are not necessary in the acute stress reaction. Thus, the immune system with its mediator substances – the cytokines – would function as a sensory organ as proposed previously by Blalock [5], by stimulating or inhibiting the various endocrine systems. In turn, in situations of prolonged elevation of IFN-α, when the initial stressor persists, glucocorticoids will act upon the immune system to prohibit exaggerated and self-destroying activiy of the immune system.

In summary, IFN-α must be added to the ever-growing list of substances with stimulating effects on the HPA axis. Adding to the results of other studies, this effect was demonstrated in vivo and in vito. It should be noted that only pharmacological doses of IFN-α were effective in vivo, so that any physiological role of IFN-α in the regulation of the HPA axis remains speculative.

Acknowledgments

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CASE REPORT Ex4

An interferon-α-induced psychotic disorder in a patient with chronic hepatitis C

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The neuropsychiatric complications of interferon-α (INF-α) treatments, as major adverse consequences of therapeutic cytokine administration, have primarily been described in the early 1980s, with the onset of interferon's therapeutic use for some malignant neoplasm and viral infections [3]. There is a considerable amount of literature on the neuropsychiatric side effects associated with INF-α, referring to depression (more frequently), personality changes, and impaired cognition; less often to psychosis and delirium; and rarely to mania [6, 8, 11]. Neurotoxicity seems to be mediated through neuroendocrine and neurotransmitter mechanisms, cytocines, and free radicals [7]. It seems that the knowledge of this kind of toxicity gives opportunities for a better understanding of the pathophysiological mechanisms of several diseases, especially while there is an increased interest concerning the possible implication of cytokines in depression [2, 9]. However, severe psychiatric manifestations represent the most important reason for the discontinuation of INF-α [11]. Adverse psychiatric effects are related to dose, duration of therapy, and route of administration [6]; they are usually reversible, though sometimes may be persistent [11].

In this paper we present the case of induced INF-α2b psychotic symptoms in a man with chronic hepatitis C one day after the administation of his standard dose of INF-α2b.

Correspondence and reprints.

CASE REPORT

A 29-year-old unmarried man was admitted to our clinic because of delusional ideas of persecution, auditory hallucinations, insomnia and psychomotor agitation. One day before admission he received his standard dose of 6 million units of INF-α2b subcutaneously. One year before and after a routine blood test, he was diagnosed for hepatitis C. The histopathological findings of a liver biopsy were suggestive of chronic hepatitis (infiltration of inflammatory cells, especially leukocytes, as well as areas with bridging necrosis). A month later he started receiving 6 million INF-α2b 3 times a week.

Cannabis abuse is reported since he was 15 years old, with heroin dependence 5 years later. The diagnosis of his infectious disease motivated him to stop using illicit drugs. He has few close friends, does not seem to enjoy emotional ties or intimate relations and spends many hours in solitary activities. According to his family's description, he is a very introverted person and never talks about his problems. The patient has a burdened psychiatric family history. His grandfather was diagnosed as schizophrenic as well as one of his first cousins.

On admission aspartate aminotransferase was 55 U/L (normal range: 0–45 U/L). Other laboratory tests were normal (complete blood cell count, glucose, urea, creatinine, alanine aminotransferase, γ-glutamyl transaminase, total bilirubin, alkaline phosphatase, cholesterol,

triglyceridia, and urine analysis). The neurologic examination was normal as well.

The patient was treated with 10 mg haloperidol im bid replaced by risperidone 3 mg bid after 3 days. Five days after admission, he had a full remission of his symptoms with a complete return to a premorbid level of functioning. The patient was discharged from hospital 10 days later, receiving risperidone 2 mg bid. He did not show any symptoms during 5 months of follow-up. INF-α2b was not reintroduced because of its association with the appearance of psychotic symptoms.

DISCUSSION

Early side effects of an INF-α treatment include a flu-like syndrome that emerges with the start of INF-α injections, whereas neuropsychiatric manifestations appear after several weeks of therapy [11]. The patient described above was receiving high doses of INF-α [10], and psychotic symptoms appeared after 11 months of continuous treatment. However, the proposition of dopamine depletion, mediated through its binding to opiate receptors, as a mechanism of INF-α-induced neurotoxicity [6] even led to clinical trials in schizophrenic patients, with inconsistent results [1, 4]. In accordance with the literature, the patient's recovery occurred a few days after the use of neuroleptics and discontinuation of INF-α2b.

Our case has some analogy to a case presented by Lemonnier et al. [5], although their patient had no psychiatric antecedent. On the other hand, our patient had a history of addictive behavior and a burdened psychiatric family history. Unfortunately, there are no clear predictive factors for the development of neuropsychiatric complications of INF-α treatments, though a previous history of psychiatric disorder, brain dysfunction or addictive behavior is usually considered as a potential contraindication for INF-α treatment [11]. This factor has not been taken into consideration in our patient's case.

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EX5

CASE REPORT

Psychosis in a methadone-substituted patient during interferon-alpha treatment of hepatitis C

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Abstract

Interferon-alpha (IFN-α) is the only effective treatment for chronic hepatitis B and C. Over 2/3 of methadone-substituted patients suffer from chronic hepatitis C but a history of psychiatric disorders or drug addiction is still seen as a contraindication for IFN-α because of a possible increased risk of severe psychiatric side effects such as depression, suicide attempts or psychotic episodes. We report on the case of a 33-year-old patient with chronic hepatitis C and a positive psychiatric history (drug abuse, borderline personality and four suicide attempts). After 4 months of therapy with IFN-α he developed a psychosis with persecution mania, complex thought disorder, disturbance of sexual identity, sleeplessness, anxiety, depression and increased irritability with suicidal thoughts. Symptoms did not disappear after discontinuation of interferon treatment. To our knowledge, there are no other reports of persistent psychosis with a possible association to interferon treatment. Development of psychosis and other psychiatric side-effects may be an indication of possible neuromodulatory effects of IFN-α with long-term treatment. On the other hand, the treatment for hepatitis C was successful. Ideas for safer treatment in methadone patients with psychiatric co-morbidity and chronic hepatitis C are needed.

Introduction

Interferon alpha (IFN-α) is the only effective treatment for chronic hepatitis B and C (Cirelli & Tyring, 1995; Haria & Benfield, 1995). However, in patients with drug abuse or methadone substitution the treatment with IFN-α is contraindicated, because further intravenous drug abuse may lead to re-infection. Additionally the high rate of psychiatric co-morbidity with increased risk of severe psychiatric side effects, such as development of depression, mania, increased irritability, changes in personality, hallucinations or delirium might complicate the treatment further (Renault & Hoofnagle, 1989;

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Muraoka *et al.*, 1996). Even sudden unexpected suicide attempts while on IFN-α have been reported, but most of them occurred in patients without psychiatric disorders (Janssen *et al.*, 1994; Gaudin *et al.*, 1995). Currently, only a few reports have tried to find risk-factors for these side-effects (Renault *et al.*, 1987; Renault & Hoofnagle, 1989; Janssen *et al.*, 1994). McDonald, Mann & Thomas (1987) identified a higher risk of patients with hepatitis and AIDS developing psychiatric side-effects from IFN-α. For patients with psychiatric co-morbidities recent studies could not confirm an increased risk. Cabrera-Gomez *et al.* (1994) treated chronic paranoid schizophrenic patients with antipsychotics and IFN-α-2b in a placebo-controlled study and patients with IFN-α had a better outcome and needed lower doses of antipsychotics than the group without. Van Thiel *et al.* (1995) have successfully treated patients with hepatitis C and drug addiction, affective or psychotic disorders in cooperation with their psychiatrists. Recently, it has also been shown that patients with hepatitis C and mood or anxiety disorders, thought of as relatively contraindicated for treatment with IFN-α, did not develop more psychiatric side-effects compared with normal controls (Pariante *et al.*, 1999). The authors found no evidence that psychiatric cases were more likely to stop IFN-α therapy than controls. Furthermore, even in a putative case of depression as a side-effect of IFN-α, effective treatment possibilities were evident (Levenson & Fallon, 1993).

Renault *et al.* (1987) described three forms of psychiatric side effects in long-term treatment with IFN-α; 17% developed organic syndromes, called organic personality syndrome, characterized by irritability and short temper, organic affective syndrome with emotional weakness, depression, fearfulness and delirium, marked by clouding of consciousness, agitation, paranoia and suicidal potential. There are a few case reports of psychotic episodes in drug users during IFN-α treatment (McDonald *et al.*, 1987; Renault *et al.*, 1987; Hendrik, 1994; Muraoka *et al.*, 1996) and they have been interpreted as flash-back psychosis, or delirium, because of earlier drug abuse. In all cases psychiatric side-effects stopped after dose reduction or discontinuation of interferon treatment.

We report on a patient in a methadone substitution programme with a positive psychiatric history and chronic hepatitis C who developed severe psychotic symptoms during therapy with IFN-α, which persisted after discontinuation of treatment.

Case report

A 33-year-old student with a history of polydrug abuse and a borderline personality disorder was treated at our hospital in 1997. The student reported continuous abuse of cannabis and LSD since he was 14 years old. In the next 2 years he used illegal drugs and developed addiction to intravenous heroin with additional abuse of cannabis, alcohol, benzodiazepines, LSD and ecstasy. In 1992 he was taken into a methadone substitution programme. During this time he occasionally used cannabis, LSD or ecstasy but there was no history of psychotic episodes. Between 1993 and 1996 he made three suicide attempts involving concurrent use of benzodiazepines and alcohol, apparently caused by difficulties in his relationships with girlfriends. Therefore, he was treated twice in a psychiatric hospital with the diagnosis of short depressive episode and borderline personality disorder. Again, there were no signs of a developing paranoid psychosis.

He was diagnosed with hepatitis C in 1989. The first liver biopsy showed a chronic active hepatitis. Four years later a second liver biopsy followed, without therapeutic consequences. In 1995, during methadone substitution, the liver biopsy was repeated and confirmed nascent fibrosis. Treatment was denied because of the psychiatric and drug history of the patient. Nevertheless, in 1996 he found a hepatologist who began treatment with IFN-α-2a (3×5 mu subcutaneous per week). During this time, methadone treatment was continued with regular urinalysis for traces of drug use.

Side effects during interferon treatment

During the first 3 weeks of the treatment he complained about an 'influenza-like' syndrome, increased tiredness, sleepiness, concentration difficulties and loss of interest, which improved during the following weeks. After 5 months the hepatologist noticed for the first time some psychopathological changes in the form of paranoia and anxiety. After 6 months he developed a complex symptomatology with loss of appetite and weight, sleepiness, anxiety, depression and

increased irritability. After 8 months his symptoms changed to delusions of persecution, suspiciousness, fear of being poisoned, loss of sexual identification, rapid changes in mood (depressive to dysphoric or aggressive behaviour) and social withdrawal with growing suicidal thoughts. Because there was no change under neuroleptic treatment with sulpirid, the patient was admitted to our hospital. When we saw the patient, he showed complex difficulties in formal thoughts. As well as the symptoms reported above, the patient was sometimes also disorientated with an inability to act logically.

Physical examination showed no major abnormalities. Blood parameters were normal, especially liver enzymes. Urinalysis was only positive for methadone and the treating physician confirmed that urinalysis was negative in the last 12 months (besides methadone). ECG, EEG and cCT were normal.

Therapy

The symptoms were interpreted as an organic psychotic episode, possibly associated with IFN-α, but the symptoms did not disappear after discontinuation of interferon treatment. Because of his paranoid, aggressive and suicidal behaviour, the patient had to be treated with antipsychotic medication (haloperidol and melperone) over 3 months. The methadone substitution was continued. Treatment was successful, but the symptoms returned after reduction of antipsychotics so that he had to take olanzapine as continuation treatment. With additional psychotherapeutic and social help, he was able to leave hospital with a reduced dose of methadone. Treatment of hepatitis was also successful, with normalization of liver parameters and a negative PCR (polymerase chain reaction for detection of viral RNA) which remained negative for 6 months as a criterion for a sustained response.

Discussion

Because of the patient's psychiatric history and ongoing methadone treatment, nearly 8 years and three liver biopsies were necessary before treatment with IFN-α was begun. However, the negative PCR result and normalized transaminases showed that the treatment was successful. From our experience this case showed typical development of side-effects caused by IFN-α: in the first 3 weeks there was a dominance of sleepiness, asthenia and concentration difficulties, disappearing after the fourth week. Severe psychiatric side effects occurred for the first time after 4 months of therapy. During months 5 and 6 symptoms could be interpreted as a mixture of organically induced deliriant and affective syndrome, combined with psychotic symptoms. Unlike other case reports, the symptoms in this case did not disappear after discontinuation of interferon treatment, an effect comparable to the concept of drug-induced paranoid psychosis in a patient with a hypothetical increased vulnerability for schizophrenia after long-term abuse of different illegal drugs. Our patient can be considered as being a 'high-risk patient' for developing psychiatric side-effects during IFN-α treatment. However, even if patients in methadone maintenance programmes often show psychiatric co-morbidities (Rounsaville *et al.*, 1982), they do not necessarily develop manifest psychotic episodes for months. Until the therapy with IFN-α was begun in our patient, there was no sign of any psychosis. Because of the lack of recent illicit drug abuse during methadone substitution, psychotic episodes cannot readily be explained as 'illegal-drug-induced' or 'flash-back' psychosis. On the other hand, from this single case we cannot conclude a direct causal relationship between IFN-α treatment and the development of psychosis. Mechanisms for the psychiatric side effects of IFN-α remain unknown. Neurotoxicity may play an important role during the first 3 weeks (Merimsky & Chaitchik, 1992; Gutterman, 1994), but possibly not for the organic syndromes after several months of treatment. There are differences in the quality and severity of early psychiatric side effects and later side-effects. Personality changes and suicide attempts are mostly reported after the third or fourth month or later with complex psychiatric changes in patients (Adams, Quesada & Gutterman, 1984; Janssen *et al.*, 1994), indicating possible neuromodulatorys effects of long-term interferon treatment. In fact, there is some evidence of an influence of IFN-α on NMDA responses through opioid receptors (Katafuchi, Take & Hori, 1995). Glutamate, acting as an excitatory amino acid (EAA) on NMDA receptors, is known to play an important role in regulating synaptogenesis and neuronal development in the central nervous system with neurotoxicity in high doses

(Meldrum & Garthwaite, 1990). Furthermore, it is posited as being involved in the pathogenesis of schizophrenia and addiction (Heresco-Levi & Javitt, 1994). However, it remains unclear if IFN-α crosses the blood–brain barrier under some conditions, or if the neuropsychiatric changes may be explained by other indirect mediators such as cytokines (IL-1, TNF) or hormonal changes (Valentine *et al.*, 1998).

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Ex 6

Note: Performing your original search, ***psychosis interferon***, in PubMed will retrieve ***103*** records.

1: Ann Pharmacother. 2003 Mar;37(3):384-7.

Psychosis associated with interferon alfa therapy for chronic hepatitis B.

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OBJECTIVE: To report a case of persistent psychosis that developed during interferon alfa (IFN-alpha) therapy for chronic hepatitis B. CASE SUMMARY: A 26-year-old man who was diagnosed with active chronic hepatitis B began treatment with IFN-alpha. Five months after initiation of therapy, he developed acute psychosis with prominent persecutory delusions and auditory hallucinations. Despite discontinuation of IFN-alpha therapy and addition of antipsychotic drug treatment, only partial recovery from psychosis was observed after 4 months of hospitalization. DISCUSSION: Unlike many previously reported cases, this patient showed only partial recovery from psychosis, despite the discontinuation of IFN therapy. Except for receiving a relatively high dose of IFN-alpha (10 million units 3 times/wk), the patient did not have any previously proposed risk factors for developing psychiatric adverse effects. The Naranjo probability scale indicates a probable relationship between the acute psychosis and IFN therapy. CONCLUSIONS: Despite its rare occurrence, psychosis can emerge during IFN-alpha therapy. This adverse effect may persist for several months, even after appropriate medical management. IFN-alpha should be used with careful monitoring of patients' psychiatric status during all stages of therapy.

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Interferon α – Induced Psychotic Disorder in a Patient with Chronic Hepatitis B

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Interferon has remained the mainstay for treating patients suffering from chronic viral hepatitis. However, its efficiency has been limited by the neuropsychiatric side effect profile that it carries; neurotransmitter alterations in the central nervous system (CNS) have been correlated to psychiatric complications of Interferon α. Although mood disorders such as depression occasionally develop during Interferon α therapy, psychotic disorders have been rarely reported. We present a case of Interferon α 2b induced psychotic symptoms in a young male with hepatitis B and review the relevant literature.

Key words: Interferon alpha, hepatitis, psychosis

INTRODUCTION

Hepatitis B has a worldwide distribution and is a major public health problem in developing countries where most people become infected with hepatitis B virus during childhood.[1,2] Around eight to ten percent of people in the general population become chronically infected.[3] The socio-economic burden of the disease on these countries is enormous. It is estimated that five to eight percent people in Pakistan are suffering from hepatitis B.[4]

Interferon has remained the mainstay of therapy for patients suffering from chronic viral hepatitis. However, its efficacy is limited by the neuropsychiatric side effect profile that it carries. It gives rise to well-documented syndromes including depression with suicidal ideation, personality changes and cognitive disturbances. Together these side-effects complicate interferon alpha therapy in 30 – 80 % of treated patients sometimes leading to cessation of therapy.[5] Modulation of opioid, serotonin, dopamine and glutaminergic neurotransmitter systems has been correlated to psychiatric complications of Interferon α.[6] Although mood disorders such as depression occasionally develop during Interferon α therapy, psychotic disorders have been rarely reported.

We present a case of Interferon α2b induced psychotic symptoms in a young male with chronic hepatitis B nine weeks after administration of a standard dose of interferon alpha 2b followed by a review of the literature.

CASE

A 19 year old male, a student by profession, presented to the gastroenterology services of the Aga Khan University Hospital, Karachi, Pakistan with a four months history of lethargy, easy fatigability, decreased appetite and a weight loss of 6 kg. History revealed that he had tested positive on screening for Hepatitis B Surface Antigen (HBsAg). Examination was unremarkable. Hepatitis Be Antigen (HBeAg) was reactive. Alanine aminotransferase (ALT) levels were elevated. Serology markers for hepatitis C and delta virus were negative. Abdominal ultrasound showed a normal sized liver with a coarse echotexture. A normal portal vein and spleen were visualized and no evidence of hepatocellular carcinoma or ascites was detected. His prothrombin time was normal and serum albumin was 4 gm/dl. Liver biopsy was not performed due to reluctance on the patient's part.

He was started on anti-viral therapy that included Interferon α2b (five million units, subcutaneously, daily for four months). Treatment continued for nine weeks without complications apart from a drop in platelet count to110 X 10E9 / L without any signs of bleeding and ALT levels improved.

Nine weeks after initiation of treatment he presented to the psychiatry services, with a two day history of confusion, disorientation and visual hallucinations. He was reported to be talking `gibberish' and was at times, incoherent. On examination, the patient was conscious but confused and perplexed, had poor concentration and was easily distractible. His approach was aggressive and he was in a delusional state. He was not oriented to time, place or person. According to the informants he had decreased appetite and sleep and was "seeing animals like lions and snakes". Past psychiatric and family history was unremarkable. Pre-morbidly he had been friendly, sociable and hard-working. Nine months into his treatment he had received 90 doses of Interferon α2b and 30 more were due. A provisional diagnosis of a sub-acute delirious episode secondary

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to Interferon α2b therapy was made and he was admitted to the hospital for further evaluation and management.

Even though he was started on a small dose (0.5mg) of Haloperidol (Serenace®), three times a day, extra-pyramidal side effects appeared shortly after initiation of treatment. Haloperidol was discontinued and the patient was started on Risperidone (an atypical antipsychotic) 0.5 mg twice a day. In consultation with his gastroenterologist, Interferon α2b therapy was withheld.

Over the next few days, he became more alert and responsive. His speech improved and became more coherent and he regained his appetite and sleep gradually. Risperidone (0.5mg twice a day) was continued and by the sixth day of admission his symptoms had resolved satisfactorily. He was discharged home with advice to follow-up in the out-patient clinic.

A follow-up visit a week later showed that he had improved clinically. He was alert and attentive and his sleep- wake cycle and appetite had returned to premorbid state. He had little recollection of his symptoms and was keen to resume his studies. Three weeks later investigations showed that his platelet counts and ALT levels were within normal limits. However, his hepatitis Be Antigen remained Reactive. He was advised to gradually decrease and then to stop Risperidone. He was subsequently seen by the gastroenterologist and it was decided to start him on Lamivudine 100mg daily orally for one year. Although his ALT levels had returned to baseline his HBeAg was still reactive and he is expected to need the anti – viral therapy for another two to three years unless he seroconverts or develops resistance to Lamivudine; in that case, he will be switched to another oral anti – viral agent.

DISCUSSION

Psychiatric symptoms related to Interferon α therapy for chronic hepatitis have been a crucial issue in consultation liaison psychiatry. Interferon α induced psychiatric symptoms primarily fall into 3 categories: 1) An organic personality syndrome characterized by irritability and short temper 2) An organic affective syndrome marked by extreme emotional lability, depression and tearfulness; and 3) A delirium-like state marked by clouding of consciousness, agitation, paranoia and suicidality.[7] Amongst psychiatric symptoms related to Interferon α use, depression with irritation and anxiety are the most commonly reported while psychotic symptoms are relatively rare.[8] These side effects usually appear after one to three months of therapy, improve within three to four days of decreasing the dose; invariably resolving once Interferon α therapy is discontinued.[7]

Interferon α induced psychiatric manifestations are widely recognized but the toxicity mechanisms are not clearly understood. The fact that this toxicity appears to be dose-dependent with variation depending on the daily dose given, the mode of administration, combination with other chemotherapy treatments, the concomitance with cerebral radiotherapy or a medical history of psychiatric illness, has been widely accepted.[9] However, few scientific studies have addressed the question of mechanism of Interferon associated neuro-psychiatric changes and yet fewer have come up with convincing explanations.

Though well known that Interferon α affects neuro-endocrine, cytokine and neurotransmitter pathways, it is not clear how that leads to the psychiatric complications.[10,11] Possible mechanisms could involve secondary cytokines and neuro – endocrine systems. Secondary cytokines may activate the hypothalamic pituitary axis, which may in turn cause depressive symptoms or persistent elevation of amines in patients treated with Interferon α providing another possible cause for depression in these cases.[12]

However, psychotic symptoms secondary to Interferon α continue to perplex researchers around the globe. Manipulation of various CNS receptors including dopamine, serotonin, opioid and glutamate receptors might give a clue as to why psychosis arises and address the reason for its rare occurrence.[6]

Review of the literature shows that Interferon α therapy should be discontinued in patients with moderate to severe suicidal ideation or those who have attempted suicide as well as in those with depression that does not respond to anti-depressant treatment in manic states and in individuals with hallucinations, delusions and delirium.[7,13,14]

On the basis of our knowledge of the pharmacological action of Interferon α, several treatment options may be suggested, but these lack empirical support at this time. Antidepressant use for this situation has been reported twice; fluoxetine[15] and nortriptyline[16] were successfully used in two patients treated with Interferon α for hepatitis C and all depressive symptoms and fatigue resolved. Naltrexone (opioid receptor antagonist) has been shown to be beneficial for cognitive impairment.[17]

For other disorders, conventional therapy has been proposed: lithium for bipolar disorders, fluvoxamine for obsessive compulsive disorders and neuroleptics for psychotic disorders.[9] Non – steroidal anti-inflammatory drugs (NSAIDs) hold a promising future for the treatment of psychiatric side effects of Interferon α.[8] Non – pharmacological interventions may also help. Education regarding possible neuropsychiatric changes secondary to Interferon α use,[17] behavioral interventions (such as distraction

and alteration of work and recreation schedules), aerobic exercises[18] and supportive psychotherapy may improve tolerance of symptoms, but currently data on these interventions is lacking.

As the incidence of hepatitis B and C induced chronic hepatitis rises in Pakistan, it is expected that more patients would be treated by Interferon. In this context, early recognition and treatment of neuro-psychiatric side-effects becomes important. This will have implications for treatment compliance as well as adequate control and remission of hepatitis.

CONCLUSION

The appearance of neuro-psychiatric side effects during chemotherapy using the Interferon α molecule is a relatively frequent complication, which at times can have serious consequences, the most important of which is discontinuation of treatment. In many cases this can prove to be fatal. Despite its relatively rare occurrence, psychosis can emerge during Interferon α therapy and its early recognition and treatment is important for a better prognosis. More basic descriptive research is needed in order to adequately design an intervention trial in this regard. This would help to prevent and treat complications and optimize Interferon α therapy in patients suffering from chronic viral hepatitis and malignancies.

NOTES ABOUT CONTRIBUTORS

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